

Experiments were done in triplicate with and without metabolic activation (S9 fractions from Aroclor-treated Sprague-Dawley rats). Results were negative in these strains.

### Clinical Management

If inhaled and breathing is difficult, the person is moved to fresh air and administered oxygen. For skin contact, the area is washed with water. For eye contact, water is used for flushing.

### Environmental Fate

Acetone is highly volatile and enters the environment mainly via the atmosphere where it may be moderately degraded by photolysis, react with photochemically produced hydroxyl radicals or be removed by wet deposition. Acetone may be biodegraded when released into the soil, but because it is miscible in water, it may leach into existing groundwater but is not expected to significantly bioaccumulate.

### Ecotoxicology

Acetone is not expected to be toxic to aquatic life. The  $LC_{50}/96\text{ h}$  values for fish are over  $100\text{ mg l}^{-1}$ .

### Other Hazards

Acetone is a volatile and an extremely flammable liquid. Vapor may cause flash fire.

### Exposure Standards and Guideline

Occupational Safety and Health Administration Permissible Exposure Limit: 1000 ppm (time-weighted average).

See also: Pollution, Air; Skin.

### Further Reading

Arts JH (2002) An analysis of human response to the irritancy of acetone vapors. *Critical Reviews in Toxicology* 32(1): 43–66.

### Relevant Websites

<http://www.atsdr.cdc.gov> – Agency for Toxic Substances and Disease Registry. Toxicological Profile for Acetone.  
<http://www.inchem.org> – Acetone: Environmental Health Criteria (from the International Program on Chemical Safety).

## Acetonitrile

Heriberto Robles

© 2005 Elsevier Inc. All rights reserved.

- CHEMICAL ABSTRACTS SERVICE REGISTRY NUMBER: CAS 75-05-8
- SYNONYMS: Cyanomethane; Ethane nitrile; Ethane-nitrile; Ethyl nitrile; Methanecarbonitrile; Methyl cyanide
- CHEMICAL/PHARMACEUTICAL/OTHER CLASS: Organic solvent; Cyanogen; Nitrile
- CHEMICAL FORMULA:  $\text{C}_2\text{H}_3\text{N}$

### Uses

Acetonitrile is used in the chemical industry as an intermediary in the synthesis of several chemicals and products such as acetophenone, thiamine, acetamidine, and  $\alpha$ -naphthaleneacetic acid,

nitrogen containing compounds, acrylic fibers, nitrile rubber, pesticides, pharmaceuticals, perfumes, and lithium batteries. It is also used as a polar solvent for both organic and inorganic compounds and in non-aqueous titrations.

### Exposure Routes and Pathways

Exposure to acetonitrile can occur through the oral, dermal, and inhalation routes. Symptoms of poisoning have been observed in persons exposed through these three routes.

### Toxicokinetics

Acetonitrile can be acutely lethal when absorbed in high doses. Acetonitrile is metabolized to a hydroxyl metabolite by cytochrome P450 in the liver. Subsequent metabolism through catalase enzymes produces hydrogen cyanide. Once metabolized, the mechanism of action is the same as expected for

cyanide poisoning. Onset of cyanide poisoning may be delayed 8 or more hours as metabolism is required to produce the cyanide metabolite. Toxicity may be prolonged for up to 3 days in some cases.

### Mechanism of Toxicity

Acetonitrile is slowly metabolized by cytochrome P450 in the liver to produce hydrogen cyanide. Toxicity is produced by the combined effect of circulating acetonitrile and cyanide. Cyanide exerts its toxicological effects by disrupting oxygen utilization at the cellular level. The disruption results in decreased oxygen utilization by body tissues and lactic acidosis.

### Acute and Short-Term Toxicity (or Exposure)

#### Animal

Animal susceptibility to acetonitrile varies by animal species and route of administration. Overall, animal susceptibility is mediated by the animal's ability to absorb and metabolize acetonitrile into its toxic metabolite, hydrogen cyanide.

Atmospheres containing up to 32 000 ppm acetonitrile are lethal to dogs. In rats, the oral LD<sub>50</sub> has been measured to range from 200 mg kg<sup>-1</sup> (in young rats) to 3800 mg kg<sup>-1</sup> (age unspecified), whereas the inhalation LC<sub>50</sub> has been determined to be 7500 ppm following an 8 h exposure. The acute dermal lethal dose has been investigated in rabbits. The LD<sub>50</sub> through the dermal route has been determined to be 980 mg kg<sup>-1</sup>. Subchronic exposures to low acetonitrile concentrations in the air (665 ppm or less) produced pulmonary inflammation and minor changes in body weights, hematocrit, hemoglobin, and liver and kidney functions.

#### Human

Toxicological effects of acetonitrile are usually delayed as the chemical has to be metabolized to cyanide. However, exposure to high doses may result in rapidly developing loss of consciousness and respiratory failure.

Signs and symptoms of exposure will be determined by the dose of acetonitrile. Onset of symptoms can be expected to be delayed from 2–12 h as acetonitrile is slowly metabolized to its toxic metabolite, cyanide. Exposure to low doses will produce nausea, salivation, vomiting, headache, and lethargy. Exposure to higher doses may produce cyanide intoxication characterized by extreme weakness, lethargy,

respiratory depression, metabolic acidosis, tachycardia, shock, coma, seizures, and possibly death.

### Chronic Toxicity (or Exposure)

#### Animal

Rats exposed to acetonitrile in air at concentrations ranging from 166 to 665 ppm for 7 h per day for up to 90 days showed no-observed-effects at doses below 330 ppm. At the maximum dose tested (665 ppm), pulmonary inflammation as well as minor kidney and liver changes were noted in some animals.

Dogs and monkeys exposed to acetonitrile in air for 91 days showed minor variations in body weight, hematocrit, and hemoglobin. The animals were dosed acetonitrile at concentrations averaging 350 ppm for 7 h day<sup>-1</sup>, 3 days week<sup>-1</sup>. Autopsy of the animals revealed some cerebral hemorrhaging as well as pigment-bearing macrophages in some animals.

Male and female rats were exposed to acetonitrile by inhalation at doses ranging from 0 to 400 ppm for 6 h day<sup>-1</sup>, 5 days week<sup>-1</sup> for 2 years. Results of the study were inconclusive regarding the carcinogenic activity of acetonitrile as there was only a marginal increased incidence of hepatocellular adenomas and carcinomas in male rats. Furthermore, there was no evidence of carcinogenic activity in the female rats even at exposures as high as 400 ppm. In a similar study using male and female mice exposed to acetonitrile at doses ranging from 0 to 200 ppm by inhalation for 6 h day<sup>-1</sup>, 5 days week<sup>-1</sup> for 2 years, no carcinogenic activity was noted in the animals and doses tested.

The toxicological effects of acetonitrile have been attributed to the direct effects of the intact molecule combined with the effects of metabolically generated cyanide ions.

#### Human

No reports were found on the chronic toxicological effects of acetonitrile in humans.

### In Vitro Toxicity Data

*In vitro* studies using rat liver microsomes have demonstrated that the conversion of acetonitrile to cyanide is mediated by cytochrome P450 (P-450IIE1).

Acetonitrile was tested for mutagenicity in the *Salmonella*/microsome preincubation assay. The tests were conducted using up to five *Salmonella* strains and in the presence and absence of rat or hamster liver S-9. All tests were negative for mutagenicity.

including those run at the maximum dose tested (10 mg per plate).

### Clinical Management

The major goal of treatment is to maintain respiration, blood circulation, and vital signs and to prevent further absorption of acetonitrile into the systemic circulation. If ingested, absorption can be prevented or minimized by instituting gastric lavage or by giving activated charcoal and a cathartic. Gastric lavage is effective only if performed soon after ingestion.

Treatment of acetonitrile poisoning is similar to that of cyanide poisoning. This includes immediate therapy with 100% oxygen and assisted ventilation, if necessary. Seizures can be controlled by giving diazepam, phenobarbital, or phenytoin intravenously at appropriate doses. Therapy should also include correction of the metabolic acidosis and to combat cyanide poisoning. Cyanide poisoning is treated by the intravenous administration of sodium nitrite and sodium thiosulfate. Care should be taken to maintain treatment for as long as acetonitrile is being metabolized to cyanide.

### Environmental Fate

If released to ambient air, acetonitrile will remain in the vapor phase where it will be degraded through reaction with photochemically produced hydroxyl radicals. The half-life of acetonitrile in ambient air has been estimated to be ~620 days. If released to soil, acetonitrile is expected to volatilize rapidly. Biodegradation in soil is not expected to be a major degradation pathway. If released to water, acetonitrile is not likely to adsorb to soil and sediment particles. Acetonitrile is expected to be removed from water bodies through volatilization as the chemical hydrolysis and bioaccumulation potential for this chemical are low.

### Ecotoxicology

Toxicity thresholds for protozoa, bacteria, and green algae have been measured to range from  $520 \text{ mg l}^{-1}$  for *Microcystis aeruginosa* (algae) to  $7300 \text{ mg l}^{-1}$  for *Scenedesmus quadricauda* (green algae).

The  $\text{LC}_{50}$  for acetonitrile in fathead minnow (*Pimephales promelas*) has been measured to be  $\sim 1640 \text{ mg l}^{-1}$  per 96 h in a flowthrough bioassay.

### Other Hazards

Acetonitrile is highly flammable and will ignite in the presence of flames, sparks, or sufficient heat. Acetonitrile vapors may combine with air to form explosive mixtures.

### Exposure Standards and Guidelines

- Occupational Safety and Health Administration permissible exposure limit =  $40 \text{ ppm}$  ( $70 \text{ mg m}^{-3}$ ).
- American Conference of Governmental Industrial Hygienists (ACGIH) 8 h time-weighted average =  $40 \text{ ppm}$ .
- ACGIH short-term exposure limit =  $60 \text{ ppm}$ .
- National Institute for Occupational Safety and Health immediately dangerous to life or health value =  $500 \text{ ppm}$ .
- The US Environmental Protection Agency's Integrated Risk Information System has published a reference concentration for acetonitrile of  $0.06 \text{ mg m}^{-3}$ .
- Florida State Drinking Water Standard =  $500 \mu\text{g l}^{-1}$ .

See also: American Conference of Governmental Industrial Hygienists; Cyanide; National Institute for Occupational Safety and Health; Occupational Safety and Health Act, US.

### Further Reading

Ellenhorn MJ and Barceloux DG (eds.) (1988) *Medical Toxicology, Diagnosis and Treatment of Human Poisoning*. New York: Elsevier.

### Relevant Websites

- <http://toxnet.nlm.nih.gov> - TOXNET, Specialized Information Services, National Library of Medicine. Search for Acetonitrile.
- <http://www.epa.gov> - Chemical Summary for Acetonitrile (from the US Environmental Protection Agency).
- <http://www.osha-slc.gov> - Safety and Health Topics: Acetonitrile (from the US Occupational Safety and Health Administration).